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TOWARDS NEW IMIDAZOLE-2-THIONE-BASED ORGANOCATALYSTS; SULFUR TRANSFER VS. DEOXYGENATION IN THE REACTION OF IMIDAZOLE N-OXIDES AND CYCLOALIPHATIC THIOKETONES

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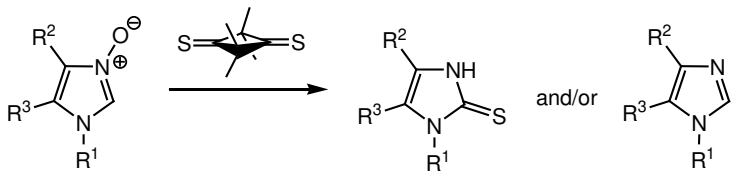
GRAPHICAL ABSTRACT



Abstract *Sulfuration or deoxygenation? Competitive transformations of the title imidazole N-oxides into respective masked thiourea analogues or into the parent heterocycle in the reaction with 2,2,4,4-tetramethylcyclobutane-1,3-dithione are presented. The influence of an electron-withdrawing substituents in combination with the steric hindrance of neighbouring groups onto reaction outcome is discussed.*

Keywords *trans*-1,2-Diaminocyclohexane, Imidazole *N*-oxides, Sulfur transfer, Deoxygenation

INTRODUCTION

In a series of recent reports, variously functionalized amino components including amino alcohols, amino acids, and α,ω-diaminoalkanes has been employed for the construction of achiral and chiral 2-unsubstituted imidazole *N*-oxides.[1] In continuation of our studies, optically pure enantiomers of *trans*-1,2-diaminocyclohexane (DACH) served as versatile scaffolds for the synthesis of C_2-symmetrical bis-imidazole derivatives **1**.[2]

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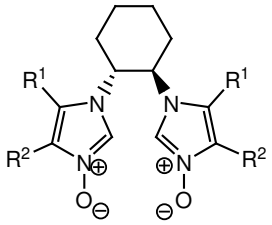


1

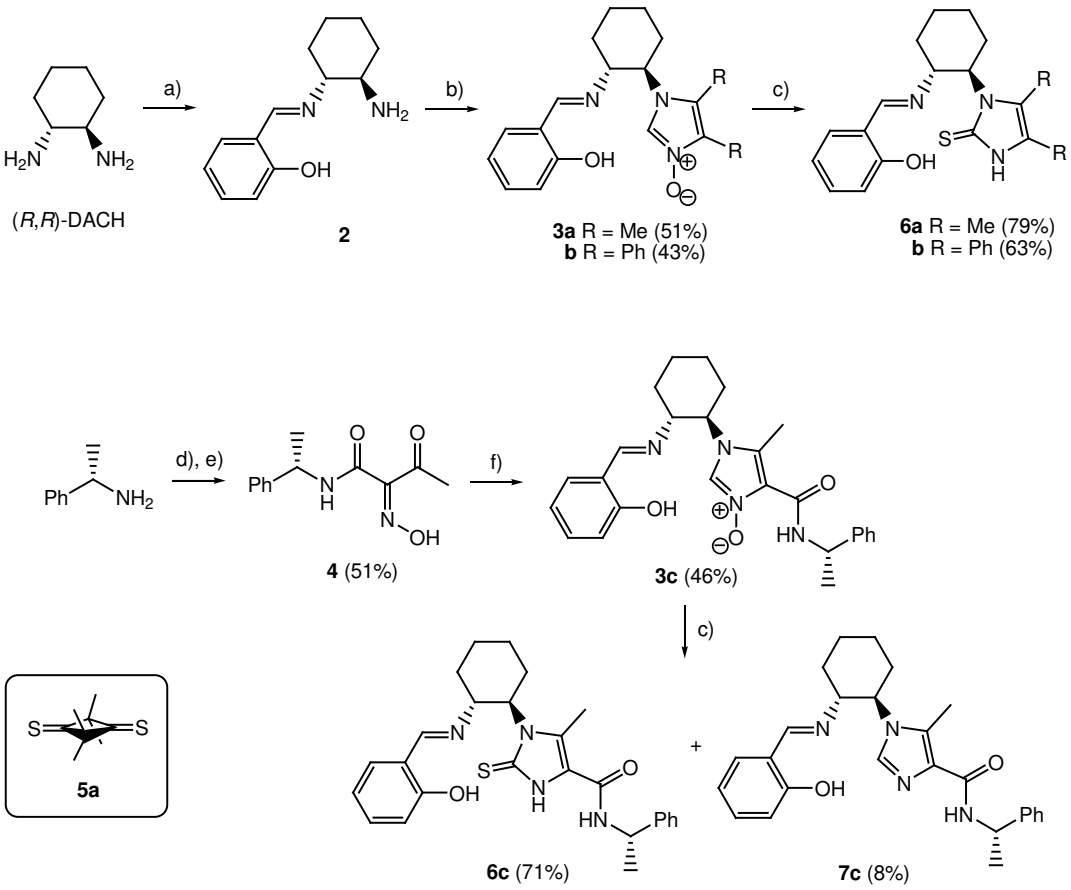
R^1,R^2 = Alkyl, Aryl, H

Figure 1 Substitution pattern of (*R*,*R*)-1,2-diaminocyclohexane-derived bis-imidazole *N*-oxides **1**.

Some of the optically active *N*,*N*'-dioxides of type **1** as well as their deoxygenated analogues were successfully applied as organocatalysts, *e.g.*, for the asymmetric allylation of aromatic aldehydes.[3] On the other hand, various thiourea derivatives act efficiently as ligands or organocatalysts for asymmetric synthesis.[4] Therefore, our ongoing studies focuses on the preparation of non-racemic imidazole-2-thiones, compounds that should be considered as masked thiourea derivatives. Since bis-imidazolethiones derived from **1** suffer from limited solubility in most of known organic solvents, we paid our attention to monoprotected derivatives of (*R*,*R*)-*trans*-diaminocyclohexane.

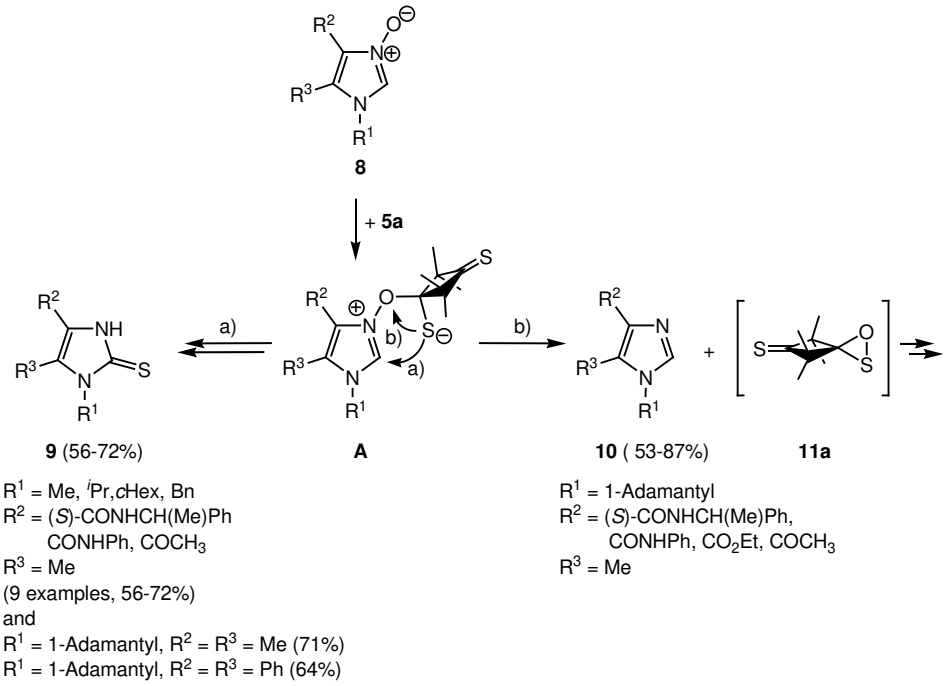
RESULTS

Although several monoprotected derivatives of DACH are readily available, the most commonly applied ones for organic synthesis, *i.e.* *N*-monoacetylated and *N*-Boc-protected analogues, failed in the preparation of desired materials. Thus, salicylaldehyde-derived monoimine **2** was studied in more detail, and under optimised reaction conditions furnished desired imidazole *N*-oxides **3a-b**. In search for a chiral α-hydroxyiminoketone substrate, *in situ* generated acetylketene was trapped by (*S*)-1-phenylethylamine to yield, after subsequent nitrosation, enantiomerically pure **4**, suitable for construction of imidazole *N*-oxide **3c** (Scheme 1).[5]



Scheme 1 Synthesis of imidazole *N*-oxides **3a-c** and their reactions with **5a**: a) salicylaldehyde (0.95 equiv.), $CHCl_3$, 0°C, 5h; b) $(CH_2O)_n$ (1.1 equiv.), EtOH, r.t., overnight, then α-hydroxyiminoketone (1.1 equiv.), reflux, 8h; c) **5a** (1.8 equiv.), $CHCl_3$, r.t., overnight; d) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (1.2 equiv.), toluene, reflux, 16 h; e) $NaNO_2$ (1.3 equiv.), AcOH, 0°C to r.t., 2.5h; f) ……

Whereas 'hemi-salen derived' imidazole *N*-oxides **3a**-**b** in the reaction with thioketone **5a** smoothly yielded the expected imidazole-2-thiones (**6a**-**b**), the presence of the electron-withdrawing carboxamide group in **3c** influenced the reaction course to give, along with the desired imidazole-2-thione **6c**, a small amount of deoxygenated compound **7c**. We assumed therefore, that the electron-withdrawing *N*-(1-phenylethyl)carboxamido group should be decisive for partial change of the reaction outcome. In order to gain more detailed information about the observed phenomena, a series of model imidazole *N*-oxides **8** were tested under the applied reaction conditions (Scheme 2).[6]



Scheme 2 Sulfur transfer *vs*. deoxygenation; a structure relationship analysis.

None of imidazole *N*-oxides of type **8** bearing an aforementioned carboxamido group at C(4) and a small (Me) or medium (*i*Pr, Bn) substituent at N(1) gave deoxygenated products of type **10**, and the respective imidazole-2-thiones **9** were isolated as sole products. In contrast, analogous N-(1-adamantyl) derivatives yielded corresponding deoxygenated imidazoles exclusively. Similar results were noticed for the C(4)-acetylated imidazole *N*-oxide series. Finally, both 1-adamantyl-4,5-dimethylimidazole *N*-oxide and its 4,5-diphenyl analogue afforded the respective sulfurated products, however, small amounts of imidazoles could also be found in mother liquor, after filtration of the major product. Thus, the structure relationship on the reaction outcome clearly indicated that the presence of an electron-withdrawing substituent at C(4) together with a bulky group at N(1) are necessary to change the reaction course. Apparently, the bulky adamantyl group causes a stepwise mechanism leading to the zwitterionic intermediate **A**, and *via* 1,3-cyclisation (route b) affords imidazole **10** accompanied by extremely reactive oxathiirane derivative **11a**. An indirect proof for the postulated formation of the oxathiirane derivative was found in a trapping experiment.[6] In the case of less hindered derivatives, the reaction occurs *via* formal [3+2]-cycloaddition and subsequent cycloreversion of the primarily formed bicyclic intermediate.[7]

The presented results summarize our recent efforts in the synthesis of enantiomerically pure imidazole-2-thiones bearing *trans*-1,2-diaminocyclohexane scaffold as well as a mechanistic proposal for the unexpected deoxygenation of the starting imidazole *N*-oxides.

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